Claims

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- 1. Process for the synthesis of isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate (Nisoldipine) comprising the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate, added to the reaction mixture in a single portion or portionwise in an apolar solvent, to give crude Nisoldipine.
- 2. The process as claimed in claim 1, wherein the apolar solvent is selected from the group consisting of aliphatic or cycloaliphatic solvents.
- 3. The process as claimed in claim 2, wherein the solvent is selected from the group consisting of cyclohexane and n-hexane.
- 4. The process as claimed in claim 1, wherein the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate and methyl 3-aminocrotonate is carried out in the presence of 4-dimethylaminopyridine.
- 5. The process as claimed in claim 1, wherein, after the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate in an apolar solvent to give crude Nisoldipine, said Nisoldipine is purified by crystallisation from a water/water soluble solvent mixture to give a pure Nisoldipine final product.
- 6. The process as claimed in claim 5, wherein the water/water soluble solvent mixture is water/acetone.
- 7. The process as claimed in claim 1, wherein, before reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate, said Nisoldipine synthesis intermediate, i.e. isobutyl 2-(2-nitrobenzylidene)acetoacetate, is obtained by reacting 2-nitrobenzaldehyde with isobutyl acetoacetate in methylene chloride, as solvent, in the presence of a catalytic amount of piperidine formate at a temperature of -10°C to 50°C.
 - 8. The process as claimed in claim 7, wherein the reaction of 2-nitrobenzaldehyde with isobutyl acetoacetate is carried out at a temperature of 20°-50°C.
 - 9. The process a claimed in claim 8, wherein the temperature ranges from 27° to 33°C.
- 10. The process a claimed in claim 7, wherein the catalyst, piperidine formate, forms in situ in the reaction mixture by addition of equimolar amounts of formic acid and piperidine.

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- 11. The process as claimed in claim 7, wherein the amount of catalyst, piperidine formate, used is 0.05-0.7 mol catalyst/mol 2-nitrobenzaldehyde.
- 12. The process as claimed in claim 11, wherein the amount of catalyst is 0.05-0.6 mol catalyst/mol 2-nitrobenzaldehyde.
- 13. The process as claimed in claim 12, wherein the amount of catalyst is 0.25 mol catalyst/mol 2-nitrobenzaldehyde.
 - 14. The process as claimed in claim 7, wherein isobutyl 2-(2-nitrobenzylidene)acetoacetate is isolated in the presence of aqueous acetic acid as solvent.
- 15. Process for the synthesis of 2-(2-nitrobenzylidene)acetoacetate including the reaction of 2-nitrobenzaldehyde with isobutyl acetoacetate in metylene chloride, as solvent, in the presence of a catalytic amount of piperidine formate, at a temperature of -10°C to 50°C.
 - 16. The process as claimed in claim 15, wherein the reaction is carried out at temperature ranging from 20° to 50°C.
 - 17. The process as claimed in claim 15, wherein the reaction is carried out at 27°-33°C.
 - 18. The process as claimed in claim 15, wherein the catalyst, piperidine formate, forms in situ in the reaction mixture by addition of equimolar amounts of formic acid and piperidine.
 - 19. The process as claimed in claim 15, wherein the amount of catalyst, piperidine formate, used is 0.05-0.7 mol catalyst/mol 2-nitrobenzaldehyde.
 - 20. The process as claimed in claim 15, wherein the amount of catalyst is 0.05-0.6 mol catalyst/mol 2-nitrobenzaldehyde.
- 21. The process as claimed in claim 15, wherein the amount of catalyst is 0.25 mol catalyst/mol 2-nitrobenzaldehyde.
 - 22. The process as claimed in claim 15, wherein isobutyl 2-(2-nitrobenzylidene) acetoacetate is isolated in the presence of aqueous acetic acid as solvent.

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